REMARKS

Claims 1-29, 31-35, 41-42 and 44-50 are pending and claims 23, 26, 29, 31, 33, 35, 41, 42 and 44 are withdrawn.

In the response filed January 7, 2008 to the Office Action of September 10, 2007 Applicant intended to amend claim 14 but did not properly annotate that C5b9 was to be deleted and C5b-9 was to be added. Applicant has therefore again amended claim 14 to improve its form and to more particularly point out the claimed invention. The amended claims are fully supported by the specification (e.g., Examples 2 and 3) and originally filed claim 14. Accordingly, no new matter has been introduced.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

DETAILED ACTION

Election/Restriction

1. Applicants acknowledge that claims 23, 26, 29, 31, 33, 35, 41, 42, and 44 are withdrawn.

Double Patenting Rejection

2-3. Claims 1-22, 24, 25, 27, 28, 32, 34, and 45-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-14 of copending application no. 11/127,438. Applicant respectfully requests that the Examiner continue to hold this provisional rejection in abeyance until allowable subject matter is identified in the instant application. Once allowable subject matter has been identified,

Applicant will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time.

Rejection Under 35 U.S.C. § 103

4. Claims 1-10, 18, 22, 24, 25, 27, 28, 32, and 34 are rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Drouin (J. Immunol. [2001] 166:2025-2032). According to the Office Action, it would have been obvious to a person of ordinary skill in the art to treat subjects with asthma using an antibody that inhibits C5 or C5a based on the teachings of Drouin. Applicant respectfully traverses this rejection.

The Drouin reference is directed to characterizing C3aR and C5aR expression on bronchial epithelial and smooth muscles cells in view of their participation in the pathology of sepsis and asthma. (See Drouin, e.g., at Abstract and page 2026, column 1, paragraph 1). Applicant reiterates that Drouin does not disclose or suggest methods for using an anti-C5 antibody as claimed herein.

Applicant understands the Examiner's position to be that the instantly claimed methods are obvious because "Drouin teaches that C5a receptors are increased on bronchial epithelial and smooth muscle cells in sepsis and in asthma...[and] that septic primates and rats treated with anti-C5a antibodies have reduced pulmonary edema and lung injury." (See Office Action at page 3). However, the Office Action later acknowledges that the authors of Drouin find expression of **C5aR is not increased on bronchial or alveolar epithelial cells in response to OVA-induced asthma**. (See Drouin at page 2031, column 1, paragraph 2 and Office Action at page 4).

The Examiner then points out that:

> Drouin's teaching of up-regulation of C5aR upregulation [sic]...is not limited to the expression of C5aR by bronchial or alveolar epithelial cells...Drouin teaches that the up-regulation of C5aR in lung is due to the "massive influx of granulocytes and macrophages[.]" (See Office Action at page 4).

Although Drouin states that "C5aR staining was detected on granulocytes and macrophages recruited to the lung as a result of the OVA challenge[,]" Applicants point out that the authors are silent regarding the significance of this observation. In fact, the absence of increased expression of C5aR on bronchial epithelial and smooth muscles cells in OVA-induced asthma – the primary focus of the reference (see above) – led the authors to conclude that:

> [a]lthough further study is required to determine the role of each receptor in these inflammatory models, ***these results suggest that both receptors contribute to lung function in the endotoxemia model, whereas C3aR may play a more significant role in lung inflammation in the asthma model.*** Recent observations that OVA-challenged C3aR-deficient guinea pigs (65) and mice (66) have reduced bronchial hyperactivity support the concept that C3aR may regulate bronchial smooth muscle function in this disease. (See Drouin at page 2031, column 1, paragraph 2; emphasis added).

In other words, their data suggests that activation of C3aR by C3a may be the more dominant mediator of lung inflammation in asthma.

One of skill in the art at the time of filing would recognize that in the complement cascade, the generation and activity of complement component C3a occurs before that of complement component C5a. This means that an inhibitor of C5 does not affect production of C3a. Accordingly, the skilled artisan reading Drouin would **not** have believed that inhibition of C5 or C5a would treat or prevent a C3a-mediated disease like asthma. Rather, the skilled artisan would have believed that inhibition of C3a or C3aR would be beneficial for treating asthma. In support of this assertion, Applicant provides Humbles et al. (Nature (2000) 406:998-1001; a copy of which is enclosed as Exhibit D and in the accompanying IDS), which is a reference published five months prior to Drouin. The reference demonstrates that mice deficient in C3aR alone were protected against methacholine-induced airway hyperresponsiveness in a mouse model of asthma. (See Humbles et al., e.g., at page 999, Figure 3). For at least these reasons, Applicant submits that the skilled artisan at the time of filing reading Drouin would not have believed inhibition of C5 would be beneficial for treating an asthma patient and thus would have had no reason to practice the claimed methods.

Furthermore, even if Drouin did disclose or suggest using anti-C5 antibodies to treat asthma, ***which it did not***, the prior art as a whole at the time of filing (as well as the post-filing references) actually taught away from benefits of using anti-C5 antibodies to treat asthma.

Applicant points out that a proper determination of *prima facie* obviousness requires that the Examiner consider ***all teachings in the analogous prior art*** and what the combined teachings would have suggested to the skilled artisan. The MPEP states that

> [w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. See MPEP § 2143.01 (II) citing *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

As evidence of the state of the art at the priority date of the application, Applicant provides Karp et al. (2000) *Nature Immunology* 1(3):221 (referred to as Karp; provided as Exhibit A and in the accompanying IDS), a reference published one year prior to Drouin. The authors of Karp found that lower expression of C5 protein is associated with more severe OVA-induced inflammation in mouse lung (see Figure 1). This discovery is in stark contrast to what a skilled artisan would have expected under the Examiner's interpretation of the Drouin publication.

In addition, Karp discloses that inhibition of C5aR results in a marked reduction in IL-12 production by monocytes *in vitro* (see Figure 3). IL-12 is a cytokine that is able to prevent or reverse experimental allergic asthma (See Abstract of Karp). This would lead one to believe that inhibition of C5 would exacerbate asthma.

Thus, Applicant submits that Karp **teaches away** from the notion that lower levels of C5 protein or activity would reduce the severity of OVA-induced inflammation in mouse lung. Accordingly, the skilled artisan reading Karp would have believed that C5 was protective against asthma and that inhibition of C5 or C5aR would not be beneficial for treating asthma.

Applicant also points out that in later publications, the authors of the Drouin reference also taught away from the use of C5 or C5aR inhibition for treating asthma. In 2006, Drs. Scott Drouin and Rick Wetsel (the first and senior author on the Drouin et al. reference, respectively) co-authored a scientific publication demonstrating a protective role for C5 in allergic airway disease. (Drouin et al. (2006) *Am J Respir Crit Care Med* 173:852-857, a copy of which is enclosed as Exhibit B and in the accompanying IDS; referred to as "Drouin 2006"). Drouin 2006 disclosed that C5-deficient mice developed more severe asthma, including increased granulocyte infiltration of the lungs, than their C5-sufficient counterparts (see Figure 2). The authors also demonstrated that administration of an anti-C5 antibody (BB5.1) resulted in increased, ***not decreased***, airway hyperresponsiveness (AHR) in acetylcholine-challenged mice (see Figure 7).

Moreover, Drs. Drouin and Wetsel co-authored an Abstract disclosing a study on AHR and airway inflammation in C5aR knockout mice (Sinha et al. (2008) *Molecular Immunology* 45:4109-4110, Abstract No. O43, a copy of which is enclosed as Exhibit C). In Sinha et al., the authors disclose that C5aR knockout mice, as well as wild-type mice treated with a C5aR antagonist, exhibited exacerbated AHR as compared to wild-type or untreated mice, respectively. The authors state that "deficiency or antagonism of the C5aR in a mouse model of pulmonary allergy causes elevated AHR[.]" (See Sinha at page 4109, paragraph 2).

To summarize, the Drouin (2001) publication cited by the Examiner sets forth an observation that C5aR expressing cells (macrophages and granulocytes) are recruited into the lung in an animal model of asthma, but no relevance is made by the authors regarding that observation, the focus of Drouin (2001) being on expression of C3aR and C5aR on lung cells themselves. Additionally, both the prior art (as exemplified by the Humbles and Karp publications) and post-filing art (as exemplified by Drouin (2006) and Sinha et al. - notably both with authors from the Drouin (2001) publication) teach away from using a C5 inhibitor to treat asthma.

Therefore, contrary to the Examiner's assertions, Drouin, together with the teachings of the prior art as a whole at the time of filing, fail to render the claims obvious. That is, in

view of the contradictory teachings of the art, the skilled artisan would not have had reason to practice the claimed methods. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

5. Claims 11-13, 15 and 16 are rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Drouin (2001; *supra*) further in view of Fitch et al. (1999) *Circulation* 100:2499-2506. The Examiner states that Drouin does not teach the treatment of human subjects and the h5G1.1 antibody, but that Fitch et al. does. The Examiner argues that is would have been obvious to a person of ordinary skill in the art to use the h5G1.1 antibody to treat airway inflammation in a human target, such as one with asthma. Applicant respectfully traverses this rejection.

Applicant incorporates the arguments presented in the prior responses in their entirety. As discussed above, the teachings of Drouin fail to render the instant claims obvious. In addition, Fitch et al. does not cure the deficiencies of Drouin as neither reference discloses or suggests that inhibition of C5 is beneficial to an asthma patient. Thus, the references taken in combination do not teach or suggest all elements of claims 11-13, 15 and 16. Accordingly, the claims are non-obvious over the cited prior art, and reconsideration and withdrawal of this rejection are respectfully requested.

6. Claims 17 and 45-48 are rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Drouin (2001; *supra*) and further in view of US Patent 4,228,795 ('795 patent) to Babington. The Examiner states that Drouin does not teach a disperser, but that the '795 patent teaches a nebulizer. The Examiner argues that is would have been obvious to a person of ordinary skill in the art to use the nebulizer taught by the '795 patent to administer the anti-C5a antibodies taught by Drouin. Applicant respectfully traverses.

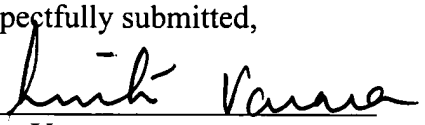
Drouin has been discussed *supra*, and the '795 patent teaches a nebulizer. Like Fitch et al., the '795 patent fails to disclose or suggest the inhibition of C5 is beneficial to an asthma patient. Accordingly, Applicant submits that the claimed methods are non-obvious over the cited prior art, and reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. Applicant does not accede to any of the Examiner's positions not specifically addressed above. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Please charge any fees or credit any overpayments to our Deposit Account No. 18-1945 from which the undersigned is authorized to draw, under order no. ALXN-P01-102.

Dated: December 8, 2008

Respectfully submitted,

By 

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